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14. ABSTRACT

The acquired coagulopathy of trauma is responsible for a large percentage of early deaths in civilian trauma practice and is a major cause of battlefield mortality. Widespread recognition has provided a rationale for fundamental changes in the initial management of severely injured patients through prevention of hypothermia, damage control surgery, massive transfusion protocols and early triage to intensive care units for optimized resuscitation. Despite these major advances, hemorrhage remains a leading cause of early death in both civilian trauma and military combat casualty care. However, it is unclear how early whole blood will affect coagulopathy in this cohort of patients as compared to the current standard of care. This study assessed if patients who require massive transfusion could be accurately predicted early after emergency department arrival and assessed if the use of stored whole blood during initial resuscitation would reduce transfusion needs compared to transfusion with component therapy and thus improve outcome. The primary clinical project has completed enrollment, randomizing 115 subjects. Additionally, the two ancillary projects have completed analysis data collected from subjects in this study to characterize the complement, platelet and immune-inflammatory response after trauma as well as the effect of adiposity after shock and resuscitation in these severely injured patients.

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Whole Blood, Trauma, Transfusion

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Introduction

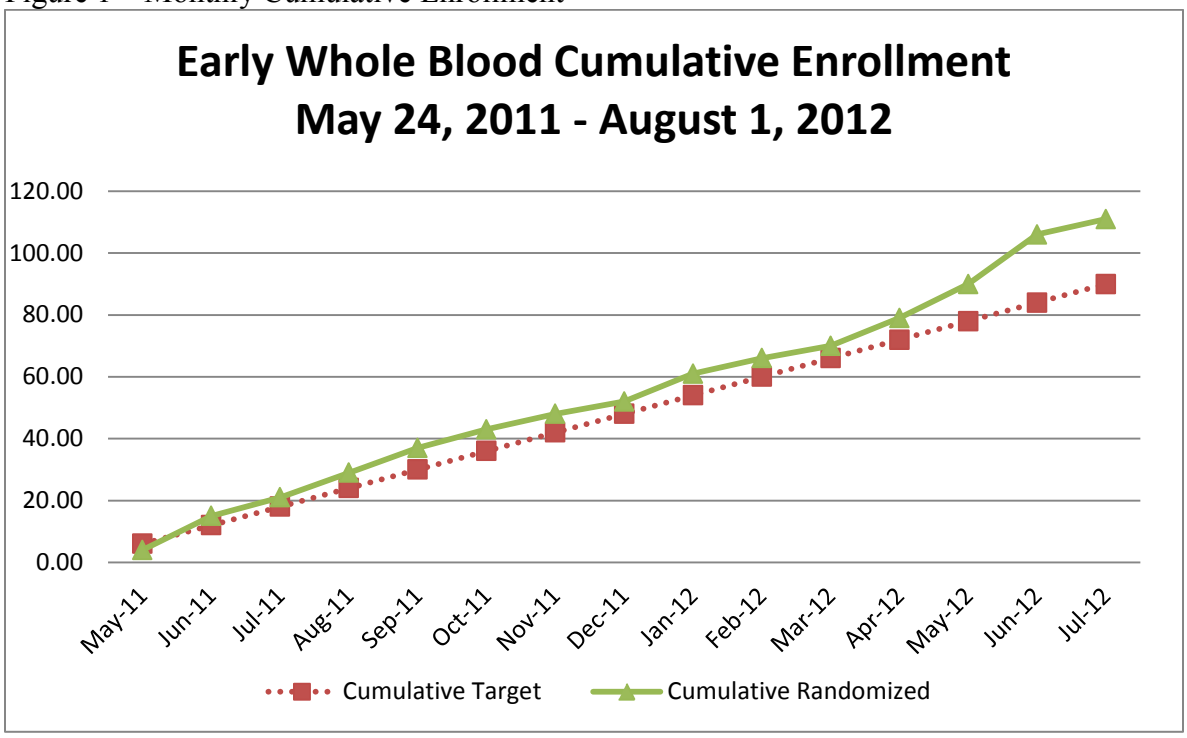
Severe uncontrollable coagulopathy in major trauma patients continues to be a major factor in trauma mortality. This project implemented a randomized, controlled trial of early whole blood transfusions in high risk, major trauma patients to determine if whole blood could prevent or control severe coagulopathy compared to standard massive transfusion care (currently 1:1 ratio of fresh frozen plasma [FFP] to packed red blood cells [PRBC]). The second goalof this proposal was to accurately predict major trauma patients who required massive transfusion within 20 minute of arrival to the emergency department (ED). Finally, this study aimed to test commonly utilized point of care assays and determine their reliability in the early prediction of transfusion needs. Two connected sub-projects under the leadership of Charles Wade, PhD, and Rosemary Kozar, MD, PhD, are associated with this project and are further discussed in the text of the report. All personnel paid on this project are listed in Appendix A.

Body

Overview

The contract was initially funded on April 1, 2007. On February 1, 2010, the study PI was changed to Bryan Cotton, MD, MPH. The Secretary of the Army approved the protocol on 14 September 2010. This trial was conducted under CFR 50.24, exception from informed consent for emergency research (EFIC). Per regulatory guidelines, 14 community consultation sessions were conducted from October 2010 to March 2011 and informed the community about this trial. Final UTHealth institutional review board (IRB) approval was obtained on March 22, 2011 and final Human Research Protection Office (HRPO) approval was obtained on March 24, 2011. The trial began enrollment on May 23, 2011. Over the course of the trial, all monthly enrollment goals were met or exceeded (Figure 1). Furthermore, three Data Safety Monitoring Board (DSMB) meetings were held where no major issues or concerns were raised. The trial concluded enrollment of August 1, 2012.

Figure 1 – Monthly Cumulative Enrollment



Primary Project (Cotton-PI)

Patients were enrolled into this study at the time blood products were ordered by the attending trauma surgeon. Patients received either whole blood (WB) or component (COMP) therapy and were monitored by direct observation for the first six hours after admission. Coagulation profiles were obtained at 3, 6, 12, and 24 hours after admission. Additional blood samples were drawn for the two sub-projects and were analyzed separately. All data involving the care of enrolled patients were entered into the Trauma Research Database which is approved by the University of Texas Health Science Center (UTHealth) Committee for the Protection of Human Subjects (CPHS). A research statistician, who remained blinded to the treatment group, evaluated the de-identified data for analysis.

AIM 1: In a prospective, randomized trial, evaluate transfusion of stored whole blood and pooled platelets during transfusion therapy.

The randomized trial began enrollment on May 23, 2011 and upon completion of the enrollment period, 1695 patients were screened and 107 were randomized, including 55 WB and 52 COMP, composing the intent-to-treat group. 81 patients received study product (39 whole blood and 42 component), composing the per-protocol group. Demographics, arrival data, initial laboratory, fluids, interventions, complications and outcomes were recorded. Three analyses were completed for this trial, intent-to-treat, per-protocol and sensitivity. In the intent-to-treat analysis, there were no differences between groups, including resuscitative fluids and mortality. As with the intent-to-treat group, no significant differences were found in the comparison of per-protocol groups, however there was a trend toward fewer units of platelet transfusions in the first three hours after arrival in the WB group. This analysis identified a disparity in non-survivable traumatic brain injury between groups, so a sensitivity analysis was conducted on the per-protocol group

excluding patients with a head abbreviated injury scale (AIS) ≥3. In this cohort all demographic and baseline data were similar between the WB and COMP groups, however 24-hour RBC, plasma and overall product usage was significantly lower in the WB group. There were no significant differences in complications or mortality between groups. See Appendix B for detailed methods and data tables in the main results manuscript published in *Annals of Surgery*.

AIM 2: Accurately predict major trauma patients who will require a blood transfusion

Prospective data for enrolled subjects were collected and analyzed. However, missingness is a serious problem within this dataset because of the severity of many patients' injuries. For many severely injured patients, patient care is rightly prioritized over recording data in the medical record by clinical staff. If the data were not recorded in the medical record, it was often difficult to retrieve when filling out the case report forms (CRFs), resulting in missing data for the study. We continue to examine the data and are working with statistical experts from Stanford and the University of California, Berkeley and clinical experts at the US Army Institute of Surgical Research (ISR) to fully achieve this aim within the next six months.

AIM 3: Test commonly utilized point-of-care analysis and determine its reliability in early prediction transfusion needs.

International normalized ratio (INR), thromboelastogram (TEG), activated clotting time (ACT), prothrombin (PT) and partial thromboplastin time (PTT) were also collected on enrolled subjects. We continue to analyze these data as well as the baseline and patient care data collected on the CRFs with the help of the experts mentioned in the previous section.

Ancillary Projects

Characterization of Complement, Platelet and Immune-inflammatory Response to Trauma (PI Wade)

Task 1: Blood samples will be collected in 2- and 3-ml citrate vials from severely injured patients upon ED arrival and periodically for up to 5 days at the ICU. Samples will be centrifuged to separate serum and plasma fractions for each sample. Samples will be frozen for future studies of complement proteins and activity, as well as immune-inflammatory biomarker identification and quantification.

This study focused on the critical first 24 hours of acute resuscitation. Timepoints of interest were chosen in collaboration with Dr. Kozar and Dr. Cotton. Samples were collected at 5 timepoints: 0, 3, 6, 12, and 24 hours, as well as 5 days. Samples were stored until the end of enrollment (August 2012). At that time, samples were shipped to collaborators at the University of California, San Francisco (UCSF), ISR and the University of Copenhagen where additional assays were conducted. UCSF performed assays related to clotting factos. ISR performed assays related to inflammatory markers and intrinsic and extrinsic pathways and microparticle profiling. Copenhagen performed assays related to markers of endothelial dysfunction. UThealth performed assays related to coagulation and platelet function by multiplate. 426 samples were collected from 71 patients. Twenty-four assays were run at each timepoint, resulting in 10,224 datafields. Preliminary analysis shows that there are minimal differences between treatment

groups. However, we are in the process of multifactorial analysis with the help of the experts from Stanford, Berkeley and ISR.

Task 2: Collection of extensive data on each study subject's demographics, type and degree of injury, and continuous physiologic, metabolic, and biochemical measures as set forth in the original IRB-approved protocol for Dr. Cotton's prime project. In addition, the patient's history before and during hospitalization in the ICU, the occurrence of sepsis, organ failure, systemic inflammatory response syndrome, and other complications of traumatic injury will be captured.

Data collection has been completed. These data are being stored in a centralized de-identified database and will be available to investigators for data mining and analysis with all other data currently being analyzed.

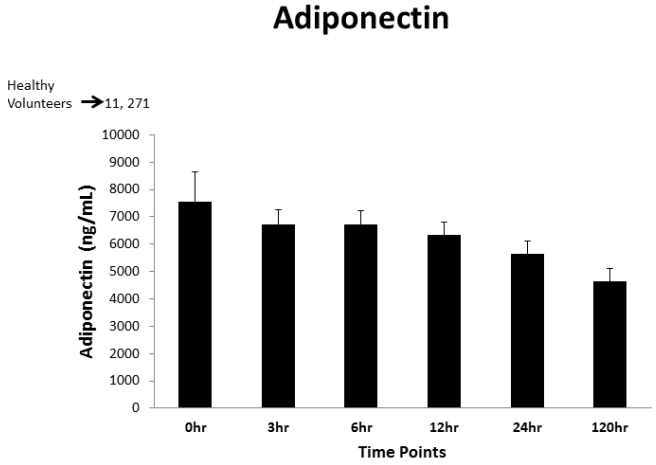
Inflammation and Adiposity after Hemorrhagic Shock and Resuscitation (PI Kozar)

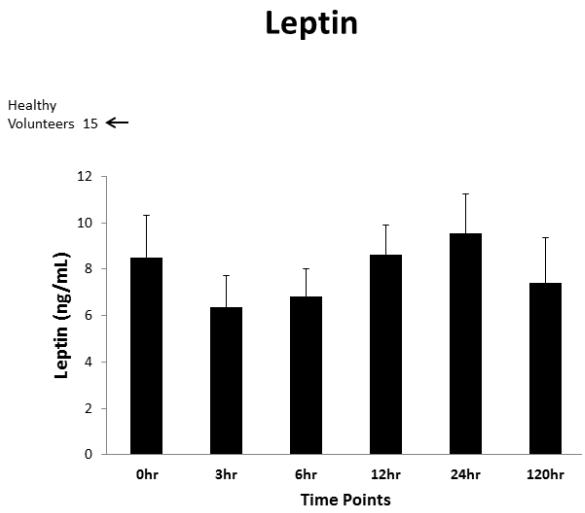
Evaluate sarcopenia based on admission CT and compare to BMI and outcomes.

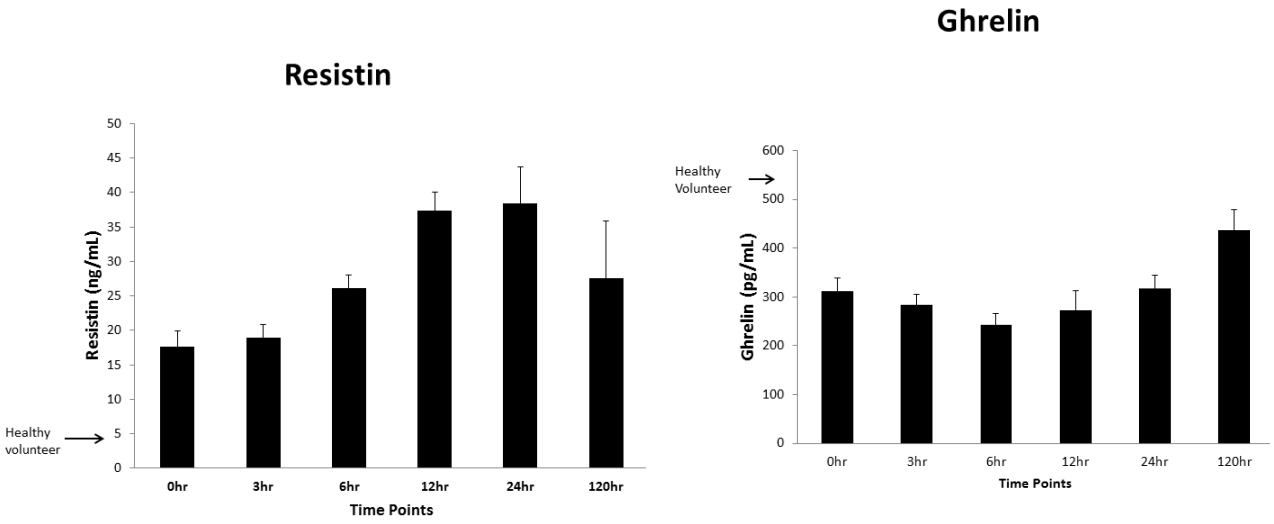
CTs from patients who were admitted to the ICU, on a ventilator, and had an admission CT scan of the abdomen are being saved on CDs and were sent to our collaborator, Dr. Mourtzakis, for calculation of sarcopenia based on muscle mass at the third lumbar vertebrae. There were 58 patients admitted to the ICU (this excludes deaths < 24 hours and those admitted to the floor or a step down unit). Of the 58 patients, 45 were intubated at least one day. Of the 45 patients that were in the ICU and intubated for at least one day, those with an abdominal CT will serve as the basis for our study. We are in the process of determining which of the 45 patients had an abdominal CT.

Measure serum (adipokines, leptin, adiponectin, and ghrelin).

We obtained serial samples thru 24 hours on 60 patients and samples thru five days on 23 patients. We measured serum adiponectin, leptin, ghrelin, and resistin, and compared values to normal healthy volunteers. Results are shown below. Statistical analysis of changes over time have not yet been completed, but adiponectin, leptin, and ghrelin were all lower in injured patients than in healthy volunteers at all timepoints. Adiponectin slowly decreased over time; leptin showed no discernible pattern of change over time; while ghrelin slightly increased by day 5. On the other hand, resistin was higher at all timepoints compared to healthy volunteers and increased over time up to day 5.







Determine nutritional adequacy for ICU patients.

In an attempt to correlate serum adipokines with nutritional adequacy, we have thus far focused our efforts on the patients with day 5 labs. Of these 23 patients, 11 were transferred out of the ICU prior to day 5. One was in the ICU but did not receive supplemental nutrition (regular diet only). That left 11 patients to assess nutritional adequacy on, which is defined as total calories and protein received/target total calories and protein x 100.

Nutritional adequacy at day 7 was only 36% (range 20-79%) for calories and 37% for protein. We are still analyzing the overall population, but preliminary results show that caloric adequacy was only 44% and protein was 45%.

Our data suggests that despite having a well-established feeding protocol and a focus on early enteral feeding, these high risk patients are being grossly underfed. Due to the small sample size (patients remaining in the ICU for at least five days), meaningful statistical analysis is not possible.

Analysis of muscle mass by CT scan in ICU patients

Skeletal muscle and adipose tissue cross-sectional areas were quantified using single slice CT scans at the third lumbar vertebra (L3). Tissue cross-sectional areas at this landmark are strongly correlated to whole body muscle and adipose tissue mass distribution. Skeletal muscle tissues quantified included the psoas, erector spinae, quadratus lumborum, transverse abdominal, internal and external obliques, and rectus abdominus and sarcopenia (low muschle mass) was identified using validated cut points. Adipose tissue compartments analyzed included subcutaneous (SAT), visceral (VAT), and intramuscular adipose tissue (IMAT); summation of these compartments allowed for quantification of total adipose tissue (TAT).

These measurements have been completed on 34 patients with an additional 25 that are pending. We have so far identified by BMI that 12 patients were of normal weight, 19 overweight, and 3 obese. Of these, six patients (17.6%) are sarcopenic, despite no patient being underweight. Analysis of adiposity is more complicated as there are not established cut points. However, we believe these data will be very interesting and we plan on correlating it with systemic levels of adipokines.

Key Accomplishments

- Screened 1695 patients
- Randomized 115 patients (54% Group A and 46% Group B)
- Completing data analysis for the main results manuscript
- Submitted final results paper for clinical trial
- Maintained all necessary regulatory approvals
- Completed clinical trial
- Publish clinical trial results paper in Annals of Surgery (Appendix B)
- 426 samples have been collected for the ancillary immune-inflammatory analysis
- Completed preliminary analysis on 60 serial samples for adipokine assessment
- Obtained preliminary results on nutritional adequacy of eligible ICU patients

Reportable Outcomes

Manuscripts

Cotton BA, Podbielski J, Camp E, Welch T, del Junco DJ, Bai Y, Hobbs R, Scroggins J, Hartwell B, Kozar RA, Wade CE, and Holcomb JB on behalf of the Early Whole Blood Investigators. A randomized controlled trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. Ann Surg. 2013;258(4):527-32; discussion 532-3.

Abstracts

Cotton BA, Podbielski J, Camp E, Welch T, del Junco DJ, Bai Y, Hobbs R, Scroggins J, Hartwell B, Kozar RA, Wade CE, and Holcomb JB on behalf of the Early Whole Blood Investigators. A randomized controlled trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. Presented at the 133rd Annual Scientific Meeting of the American Surgical Association. Indianapolis, IN. April 4-6, 2013.

Dalle Lucca J, Slack J, Cohen MJ, Cotton BA, Holcomb JB, Dubick MA, Baer LA, Cardenas JC, CE Wade and the EWB Study Group. Presented at the Annual Military Health System Research Symposium (MHSRS), August 12-15 2013. Ft. Lauderdale, Florida.

Cotton BA, Podbielski J, Camp E, Welch T, del Junco DJ, Bai Y, Hobbs R, Scroggins J, Hartwell B, Kozar RA, Wade CE, Holcomb JB and the EWB Study Group. Findings of the modified whole blood study: A randomized controlled trial of modified whole blood versus component therapy. Presented at the Annual Military Health System Research Symposium (MHSRS), August 12-15 2013. Ft. Lauderdale, Florida.

There are no other reportable outcomes to report.

Conclusions

The final results of the clinical trial have been published in the October 2013 issue of *Annals of Surgery*. From the data collected, we can conclude that WB therapy did not reduce transfusion volumes in severely injured patients predicted to receive a massive transfusion when compared to component therapy. Furthermore, no differences were reported in 24-hour and 30-day mortality. However, WB significantly reduced red blood cell, plasma and overall transfusion volumes in patients that did not have a severe traumatic brain injury. We are currently in the process of completing the follow-ups to the community consultation process to report the findings of the trial to the public. As we have previously reported, we have been able to capture and define those patients, provide and system issues experienced in carrying out a randomized trial of patients with life-threatening bleeding. We have been able to use the experience from this trial to progress forward and with another randomized clinical trial in this severely injured patient population. Additional analyses are being performed on ancillary studies with statistical experts from Stanford and the University of California, Berkeley and should be completed in the next six months, resulting in additional publications.

References

None

Appendices

Appendix A- List of paid personnel

Jeanette Podbielski

Zeinab Alawadi

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Mary Elopre

John Holcomb

Debra Rollo

Rishika Sharma

Binod Shrestha

Charles Wade

Kechen Ban

Rosemary Kozar

Appendix B– Annals of Surgery Publication

A Randomized Controlled Pilot Trial of Modified Whole Blood versus Component Therapy in Severely Injured Patients Requiring Large Volume Transfusions

Bryan A. Cotton, MD, MPH,† Jeanette Podbielski, BSN,† Elizabeth Camp, MSPH,† Timothy Welch, NREMT-P,† Deborah del Junco, PhD,† Yu Bai, MD, PhD,‡ Rhonda Hobbs, MT (ASCP),‡ Jamie Scroggins, MT (ASCP),§ Beth Hartwell, MD,§ Rosemary A. Kozar, MD, PhD,* Charles E. Wade, PhD,*† and John B. Holcomb, MD*† on behalf of The Early Whole Blood Investigators*

Objectives: To determine whether resuscitation of severely injured patients with modified whole blood (mWB) resulted in fewer overall transfusions compared with component (COMP) therapy.

Background: For decades, whole blood (WB) was the primary product for resuscitating patients in hemorrhagic shock. After dramatic advances in blood banking in the 1970s, blood donor centers began supplying hospitals with individual components [red blood cell (RBC), plasma, platelets] and removed WB as an available product. However, no studies of efficacy or hemostatic potential in trauma patients were performed before doing so.

Methods: Single-center, randomized trial of severely injured patients predicted to large transfusion volume. Pregnant patients, prisoners, those younger than 18 years or with more than 20% total body surface area burns (TBSA) burns were excluded. Patients were randomized to mWB (1 U mWB) or COMP therapy (1 U RBC+ 1 U plasma) immediately on arrival. Each group also received 1 U platelets (apheresis or prepooled random donor) for every 6 U of mWB or 6 U of RBC + 6 U plasma. The study was performed under the Exception From Informed Consent (Food and Drug Administration 21 code of federal regulations [CFR] 50.24). Primary outcome was 24-hour transfusion volumes.

Results: A total of 107 patients were randomized (55 mWB, 52 COMP therapy) over 14 months. There were no differences in demographics, arrival vitals or laboratory values, injury severity, or mechanism. Transfusions were similar between groups (intent-to-treat analysis). However, when excluding patients with severe brain injury (sensitivity analysis), WB group received less 24-hour RBC (median 3 vs 6, $P = 0.02$), plasma (4 vs 6, $P = 0.02$), platelets (0 vs 3, $P = 0.09$), and total products (11 vs 16, $P = 0.02$).

Conclusions: Compared with COMP therapy, WB did not reduce transfusion volumes in severely injured patients predicted to receive massive transfusion. However, in the sensitivity analysis (patients without severe brain injuries), use of mWB significantly reduced transfusion volumes, achieving the prespecified endpoint of this initial pilot study.

Keywords: hemorrhagic shock, resuscitation, transfusion, trauma, whole blood

(*Ann Surg* 2013;258:527–533)

From the Departments of *Surgery, †Center for Translational Injury Research, and ‡Pathology and Laboratory Medicine, University of Texas Health Science Center, Houston, TX; and §Gulf Coast Regional Blood Center, Houston, TX.

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Disclosure: No other support was used and the authors have no conflicts or other financial disclosures.

This study was registered with ClinicalTrials.gov as NCT01227005.

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With the birth of blood banking during World War I, whole blood (WB) quickly became the preferred product for resuscitating patients in hemorrhagic shock.[1] WB continued to be the primary resuscitation fluid in military settings through the beginning of the Vietnam War, with glucose and saline solutions reserved for dehydration and diarrhea.[2,3] However, after dramatic advances in component separation in the 1960s and the 1970s, blood donor centers began supplying hospitals with individual components [red blood cells (RBCs), plasma, platelets] and removed WB as a readily available product. Although some studies suggested noninferiority in elective surgical cases, no studies of efficacy or hemostatic potential for patients in hemorrhagic shock were performed before these changes.[4–6] During this period, resuscitation paradigms were further "diluted" with increased use of crystalloids and aggressive catheter-directed strategies.[7] Not surprisingly, the acute coagulopathy of trauma, abdominal compartment syndrome, and adult respiratory distress syndrome began to be identified with increasing frequency.[8–10]

For the next 20 years, the trauma community at large avoided the use of plasma and platelets on the basis of studies from the 1960s and the 1970s (when WB-based transfusions were available); we failed to appreciate the differences between the products used in the studies supporting these guidelines and those that were now available.[11] The work of resuscitation giants such as Carrico and Shires[12] supported the use of saline for hemorrhagic shock "until whole blood is available." Similarly, other landmark articles demonstrated that platelet and plasma transfusions in trauma were unnecessary "as a supplement for whole blood transfusions in bleeding patients."[13,14] This pilot study set out to assess the use of WB for early resuscitation of civilian patients with trauma. Specifically, we hypothesized that resuscitation of severely injured patients with modified whole blood (mWB) would result in fewer overall transfusions compared with component (COMP) therapy.

METHODS

Study Setting

The Texas Trauma Institute at Memorial Hermann Hospital is an American College of Surgeons–verified level I trauma center. Memorial Hermann is the primary teaching hospital for the University of Texas Health Science Center.

Regulatory Oversight and Approval

This study was conducted under the Exception From Informed Consent for Emergency Research, 21 CFR 50.24. The University of Texas Health Science Center at Houston and the Memorial Hermann Hospital Institutional Review Boards approved this study. Per 21 CFR 50.24, Community Consultation was performed before beginning the study that allowed for randomization of the patient and initiation of the protocol.

Patient Population

Patients were included in the study if they appeared to be 18 years of age or older, met highest-level trauma activation criteria, and had evidence of active bleeding requiring emergent uncrossmatched blood while in the emergency department (ED). Patients were excluded from the study if the patients received more than 4 units of RBC prerandomization, were moribund (cardiopulmonary resuscitation [CPR] or ED thoracotomy prerandomization), had noted religious objection to transfusion, had do not resuscitate (DNR) order documented, were "obviously pregnant," were incarcerated/prisoners, or had an "opt-out" bracelet.

Three other critical exclusions were added to the study protocol after initial protocol development and approval on the basis of a pragmatic design. First, in those clinical situations in which the physician stated that the patient could not wait the additional time for blood typing (an additional 5–10 minutes to the first cooler's arrival), the patient was excluded and standard of care massive transfusion (MT) protocol delivered. Second, as less than 10% of donors to our regional blood center are group B and AB blood types, availability of such products in WB form for our study was in limited supply. As such, these blood groups (B and AB) were excluded from the study after typing and standard of care MT coolers were released. Finally, although we did not list severe traumatic brain injury (TBI) in our exclusion criteria, it was not our intent to include this patient population. Therefore, when we noted that a significant number of patients with severe TBI were being enrolled early in the study, we met with trauma faculty and requested that they take increased efforts to identify and exclude patients whom they felt might have sustained severe TBI. Only 2 patients with severe TBI were enrolled after this intervention and added exclusion.

Intervention, Randomization, and Blinding

This is a single-center, randomized controlled trial of modified whole blood versus standard component therapy (red blood cells, plasma, and platelets) in the early resuscitation of injured patients presenting with evidence of hemorrhagic shock and predicted to receive a large volume transfusion. Patients who met inclusion criteria were randomized in a 1:1 fashion to either WB group transfusions or COMP therapy (COMP group). After randomization, a study cooler was released from the blood bank. Each WB cooler group contained 6 units of WB, whereas each COMP cooler contained 6 units of RBC and 6 units of plasma. In addition, both groups received a room temperature tackle box containing 1 apheresis platelet with each study cooler.

Upon meeting inclusion criteria, research personnel notified the trauma faculty of eligibility and contacted the blood bank directly. Blood bank personnel then randomized the patient by opening a sealed envelope with the assigned study group (WB or COMP). The products were released to the ED tech who returned the products to the patient's bedside (intention-to-treat group). The products remained sealed (and all personnel outside the blood bank blinded) until trauma faculty ordered subsequent transfusion. Once the seal of the cooler was broken, the patient was considered enrolled in the study (per-protocol group) and study and clinical personnel were then unblinded to treatment group. Patients remained on protocol until (1) declaration of hemostasis, (2) death, (3) withdrawal from the study (legal authorized representative [LAR] or patient refusal to continue) or (4) up to 24 hours postenrollment. At that point, should the patients require additional products, transfusions were as directed by the physician in charge of their care.

Description of Study Products

Gulf Coast Regional Blood Center provided all blood products. All units of blood for each study group were typed and crossmatched, leukoreduced, and underwent standard infectious disease testing.

Despite the controversy surrounding leukoreduction, the funding agency's institutional review board (US Army Human Research Protections Office) required that all RBC and WB units be leukoreduced.[15,16] As such, platelets in the WB units were rendered nonfunctional (and cleared) by the leukoreduction filter. In addition, WB units were kept at 1 to 6°C for up to 5 days also making the platelets nonfunctional via gross aggregation.[17] Therefore, every 6 units of WB (as with every 6 units of RBC and plasma) were supplemented with 1 dose of apheresis platelets.

Outcome Measure

The primary outcome of interest in this "first of its kind" pilot study was 24-hour blood product use. This was defined as total RBC, plasma, and platelets transfused in the first 24 hours. Each WB unit was assigned a value of 1 unit of RBC and 1 unit of plasma. Secondary outcomes of interest included 24-hour and 30-day mortality, and length of stay, transfusion associated complications, and infections.

Data Collection

Dedicated research personnel in hospital 24/7 collected prehospital data immediately on arrival. Data obtained in the ED, operating room, interventional radiology, and intensive care unit (in the first 24 hours) were collected through direct observation and in a "real-time" fashion. Data after 24 hours were collected daily through electronic and paper medical record queries.

Definitions

"Prerandomization blood products" were defined as all products received before arrival of the study cooler and tackle box. "Multiple organ failure" was defined using the Denver multiple organ failure scoring system.[18] "Infectious complications, severe sepsis, and septic shock" were defined in accordance with the guidelines of the American College of Chest Physicians and the Society of Critical Care Medicine.[19,20] "Transfusion-related acute lung injury" was defined by the documentation of acute hypoxemia with Pao_2/Fio_2 ratio of less than 300 mm Hg, bilateral infiltrates by chest radiograph (CXR) (in the absence of left atrial hypertension), and the no evidence of acute injury before transfusion. Onset of transfusion-related acute lung injury was required to have occurred within 6 hours of the last transfusion. "Nonsurvivable TBI" was defined by (1) the presence of a severe TBI upon admission and (2) the documentation by neurosurgical faculty of a nonsurvivable nature of the head injury or the declaration of brain death.

Sample Size and Power Calculation

The sample size calculation was based on the primary outcome (number of units transfused within the first 24 hours or in-hospital resuscitation. At the time of the sample size calculation, studies published on the use of predefined MT protocols demonstrated a potential reduction in 24-hour blood product use of 4 to 5 units.[21,22] Based on the sample size calculations performed, a sample size of 66 patients per group had a power of 90% with a 2-tailed α of 0.05 to detect a difference of 4 units between the 2 groups.

Data Analysis

The primary study analysis was an intent-to-treat analysis that included all patients who met inclusion criteria, were randomized by the blood bank, and had study products delivered to their bedside for

transfusion. Secondary analysis evaluated the per-protocol group. In addition, a sensitivity analysis was performed to address the initial inclusion of patients with severe TBI. Patients with head abbreviated injury scale (AIS) score of 3 or greater were excluded from this analysis.

Continuous data are presented as medians with 25th and 75th interquartile range (IQR), with comparisons between groups performed using the Wilcoxon rank sum test (Mann-Whitney *U* test). Categorical data are reported as proportions and, where appropriate, tested for significance using χ^2 or Fisher exact tests. All statistical tests were 2-tailed, with $P < 0.05$ set as significant.

STATA Statistical software (version 12.1; College Station, TX) was used for analysis.

RESULTS

During the study period, 1695 patients were screened (Fig. 1). Of these, 1338 were initially excluded because of ineligibility (1241 due to inclusion failure and 97 from meeting exclusion criteria). A total of 357 eligible patients were then evaluated, of which 250 patients were excluded: 25 for blood type (not A or O group), 8 for receiving more than 4 RBC prerandomization, 38 had no trauma faculty present on arrival, 136 had trauma faculty unable to wait for type-specific product, and 43 had likely severe TBI. This left 107 patients who were randomized into the study.

Intent-to-Treat Analysis

A total of 55 patients were assigned to the mWB arm and 52 to the COMP arm, thereby composing the intent-to-treat group. There were no demographic differences between these groups (Table 1). There were no differences in mechanism of injury (69% blunt in mWB vs 67% in COMP; $P = 0.84$), nor method of transport (71% of mWB arrived by helicopter vs 65% of COMP; $P = 0.60$) Although arrival vital signs and overall injury severity were similar, the mWB group did demonstrate a trend toward lower arrival Glasgow Coma Scale scores ($P = 0.11$) and higher head AIS score (median 0 with 0 and 3 IQR vs 0 with 0 and 2 IQR, $P = 0.14$). Initial trauma laboratory values were similar with a trend toward higher international normalized ratio in the mWB subjects ($P = 0.14$).

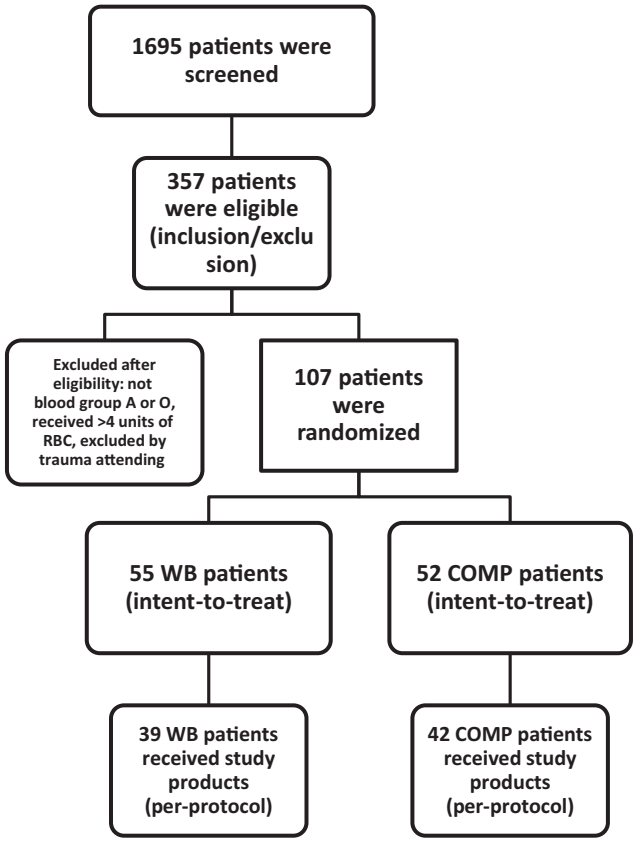

FIGURE 1. Study design and patient selection.

TABLE 1. Demographic, Arrival Data, and Initial Laboratory Values Comparison of Intent-to-Treat and Per-Protocol Groups

	mWB Group	COMP Group	
Intent-to-Treat Group			***P***
n	55	52	
Median age, yr	40 (29, 56)	38 (25, 56)	0.49
Male sex (%)	78	83	0.56
White race (%)	60	52	0.40
Median arrival GCS	5 (3, 15)	14 (3, 15)	0.11
Median arrival SBP, mm Hg	97 (80, 110)	96 (81, 114)	0.93
Median arrival HR, bpm	101 (78, 131)	102 (87, 132)	0.82
Median ISS	22 (13, 34)	22 (14, 32)	0.55
Median hemoglobin, g/dL	12.2 (10.6, 13.8)	12.5 (11.5, 13.6)	0.50
Median base value	−6 (−3, −11)	−5 (−2, −9)	0.24
Median INR value	1.2 (1.1, 1.4)	1.1 (1.0, 1.3)	0.14
Per-Protocol Group			
n	36	41	
Median age, yr	39 (26, 56)	38 (29, 52)	0.92
Male sex (%)	81	90	0.23
White race (%)	64	49	0.19
Median arrival GCS	3 (3, 15)	14 (3, 15)	0.08
Median arrival SBP, mm Hg	96 (80, 110)	91 (80, 113)	0.64
Median arrival HR, bpm	101 (80, 135)	101 (87, 128)	0.99
Median ISS	24 (14, 36)	22 (15, 34)	1.00
Median hemoglobin, g/dL	12.0 (11.1, 13.7)	12.1 (10.9, 13.5)	0.60
Median base value	−6 (−3, −11)	−6 (−2, −10)	0.51
Median INR value	1.3 (1.1, 1.4)	1.1 (1.1, 1.3)	0.13

Continuous values are presented as median with 25th and 75th interquartile range.
GCS indicates Glasgow Coma Scale; HR, heart rate; INR, international normalized ratio; ISS, injury severity score; SBP, systolic blood pressure.

There were no differences in 24-hour RBC, plasma or platelet use between the 2 study groups. There was also no difference in median 24-hour volumes (3680 mL in the mWB group and 3920 mL in the COMP patients, $P = 0.462$.) Prerandomization RBC and plasma were similar (median 3 vs 3, $P = 0.81$). However, there was a trend toward less plasma and platelet transfusions in the first 3 hours after arrival among mWB subjects ($P = 0.11$ and 0.08, respectively) (Table 2). Both 24-hour and 30-day mortality were similar between the 2 groups. The most common cause of death in the WB arm was nonsurvivable TBI, whereas exsanguination accounted for the majority of deaths in the COMP subjects (Table 3). The median time to death in the mWB group was 12.9 hours (IQR of 3.9 and 71.4) compared with 4.5 hours in the COMP group (IQR of 1.5 and 20.3); $P = 0.512$. Although there was no statistical difference in time to death between groups, this may represent type II error.

TABLE 2. Primary and Secondary Outcome Differences Among Intent-to-Treat and Per-Protocol Groups

	WB Group	COMP Group	
Intent-to-Treat Group			***P***
n	55	52	
Median 24-hr RBC transfusions, U	4 (2, 8)	6 (2, 11)	0.78
Median 24-hr plasma transfusions, U	4 (2, 8)	4 (2, 10)	0.71
Median 24-hr platelet transfusions, U	0 (0, 1)	0 (0, 2)	0.41
Median 24-hr total transfusions, U	12 (6, 24)	13 (5, 29)	0.61
24-hr mortality, %	11	10	0.83
30-d mortality,%	22	14	0.26
Per-Protocol Group			
n	36	41	
Median 24-hr RBC transfusions, U	6 (3, 9)	6 (4, 13)	0.68
Median 24-hr plasma transfusions, U	6 (3, 12)	6 (4, 13)	0.91
Median 24-hr platelet transfusions, U	1 (0, 2)	1 (0, 2)	0.76
Median 24-hr total transfusions, U	17 (11, 29)	18 (8, 37)	0.99
24-hr mortality, %	16	12	0.58
30-d mortality, %	27	15	0.16

Continuous values are presented as median with 25th and 75th interquartile range.

TABLE 3. Comparison of Causes of Death Among Intent-to-Treat Patients

	WB Group (n = 12)	COMP Group (n = 7)	*P*
Nonsurvivable TBI	8 (67%)	3 (43%)	0.46
Exsanguination	3 (25%)	4 (57%)	0.31
Sepsis	0 (0%)	0 (0%)	1.00
Multiple organ failure	1 (8%)	0 (0%)	0.61

With respect to complications between mWB and COMP subjects, there were no differences in ventilator-dependent respiratory failure (29% vs 33%, $P = 0.68$), adult respiratory distress syndrome (0.0% vs 1.9%, $P = 0.32$), infectious complications (20% vs 17%, $P = 0.72$), severe sepsis/septic shock (4.5% vs 2.0%, $P = 0.35$), acute kidney injury/acute renal failure (2.0% vs 1.5%, $P = 0.53$), multiple organ failure (7.6% vs 9.0%, $P = 0.79$), or abdominal compartment syndrome (1.8% vs 1.9%, $P = 0.97$). There were no cases of transfusion-related acute lung injury in either group. There were no differences in congestive heart failure (1.8% vs 0.0%, $P = 0.33$) or new onset arrhythmias requiring intervention (5% vs 2%, $P = 0.34$). There were also no cerebrovascular events, myocardial infarctions, or acute coronary syndromes in either group.

When comparing length of stay between mWB and COMP subjects, there were no differences in hospital-free days (median 15 days, 25th and 75th IQR of 4 and 23 vs 16 days, IQR of 7 and 23; $P = 0.85$), intensive care unit–free days (median 30 days, IQR of 11 and 30 vs 29 days, IQR of 17 and 30; $P = 0.89$), or ventilator-free days (median 30 days, IQR of 26 and 30 vs 30 days, IQR of 26 and 30; $P = 0.35$).

Per-Protocol Analysis

Thirty-nine WB patients and 42 COMP patients actually received study products, composing the per-protocol group (Table 1). As with the intent-to-treat group, there were no differences in demographics or baseline data. Similarly, there were no differences in mechanism of injury (67% blunt in mWB vs 66% in COMP; $P = 0.94$), nor method of transport (72% blunt in mWB vs 66% in COMP; $P = 0.58$) Again, a trend was noted in the mWB group with respect to lower admission Glasgow Coma Scale score ($P = 0.08$) and higher initial international normalized ratio ($P = 0.13$).

There were no differences in 24-hour RBC, plasma, or platelet use between the 2 per-protocol groups (Table 2). However, there was a trend toward less platelet transfusions in the first 3 hours after arrival among mWB subjects ($P = 0.06$) Both 24-hour and 30-day mortality were similar between the 2 groups. The disparity in nonsurvivable TBI between groups was again observed and likely accounts for the difference observed in 30-day mortality (although not significant). Nonsurvivable TBI was the cause of death in 60% of mWB subjects vs 33% of COMP patients ($P = 0.29$). Exsanguination accounted for 30% of mWB deaths compared with 67% for those in the COMP arm ($P = 0.14$).

Sensitivity Analysis (Excluding Patients With Severe TBI)

The sensitivity analysis was conducted among those patients who received study products (per-protocol) and did not have severe TBI. Among these, 33 WB patients and 34 COMP patients were evaluated (Table 4). There were no differences in demographics or baseline data. No differences in mechanism of injury (64% blunt in mWB vs 59% in COMP; $P = 0.68$) or method of transport (53% blunt in mWB vs 52% in COMP; $P = 0.94$) were observed.

Among this cohort of patients, 24-hour RBC, plasma, and overall product use were significantly lower in the mWB group (Table 5). In addition, 24-hour platelet use demonstrated a trend toward decreased transfusion among the mWB subjects ($P = 0.09$).

TABLE 4. Demographic, Arrival Data, and Initial Laboratory Values Comparison of Sensitivity Analysis Groups (Head AIS Score ≥3 Excluded)

	WB Group (n = 33)	COMP Group (n = 32)	*P*
Median age, yr	38 (28, 55)	39 (27, 52)	0.74
Male sex (%)	85	87	0.76
White race (%)	52	53	0.93
Arrived by helicopter (%)	64	59	0.68
Blunt mechanism of injury (%)	53	52	0.94
Median arrival GCS	15 (3, 15)	15 (14, 15)	0.36
Median arrival SBP, mm Hg	98 (85, 110)	99 (76, 113)	0.60
Median arrival HR, bpm	104 (83, 135)	105 (87, 130)	0.91
Median ISS	14 (19, 25)	18 (14, 25)	0.51
Median hemoglobin, g/dL	12.3 (10.5, 14.1)	12.5 (10.8, 13.5)	0.97
Median base value	−6 (−3, −11)	−5 (−2, −9)	0.12
Median INR value	1.2 (1.1, 1.4)	1.1 (1.1, 1.2)	0.82

Continuous values are presented as median with 25th and 75th interquartile range.

GCS indicates Glasgow Coma Scale; HR, heart rate; INR, international normalized ratio; ISS, injury severity score; SBP, systolic blood pressure.

TABLE 5. Sensitivity Analysis Evaluating the Primary and Secondary Outcomes in Those Patients Without Severe TBI

	WB Group (n = 33)	COMP Group (n = 34)	*P*
Median 24-hr RBC transfusions, U	4 (2, 6)	6 (2, 13)	0.02
Median 24-hr plasma transfusions, U	4 (2, 7)	6 (2, 14)	0.02
Median 24-hr platelet transfusions, U	0 (0, 1)	1 (0, 2)	0.09
Median 24-hr total transfusions, U	11 (5, 17)	16 (4, 41)	0.02
24-hr mortality, %	6%	9%	0.62
30-d mortality, %	6%	9%	0.62

Continuous values are presented as median with 25th and 75th interquartile range.

Prerandomization RBC and plasma were again similar (median 3 vs 3, $P = 0.89$). Both 24-hour and 30-day mortality were similar between the 2 groups. The median time to death in the mWB group was 11.7 hours (IQR of 3.9 and 135.4), whereas that of the COMP group had a time to death of 1.9 hours (IQR of 1.1 and 4.5); $P = 0.149$. This as well may represent a type II error.

DISCUSSION

Before the 1980s, WB was the primary resuscitation product for patients in hemorrhagic shock. However, with the widespread implementation of COMP therapy, saline solutions and packed RBCs quickly replaced WB.[4,5,23] However, the US military has used WB in every conflict since World War I and did so again in 1993 in Somalia.[24] In 2001, US military forces were deployed to Iraq and Afghanistan and began using WB with increased frequency.[25,26] Data from these conflicts demonstrated that fresh WB was independently associated with a decreased blood product use and mortality. Soon after, WB was added to the Department of Defense's (DoD's) 's transfusion algorithm for severely injured casualties, with more than 10,000 units transfused to US personnel to date.[27] These experiences led to a consensus statement from military and civilian surgeons and physicians to dramatically rethink the resuscitation of hemorrhagic shock.[28] Damage control resuscitation soon emerged, promoting earlier and more aggressive use of plasma and platelets, in ratios approximating that of WB. This charge was consistent with that of investigators who had previously advocated for supplementation of hemorrhagic shock resuscitation with plasma rather than crystalloid or standard colloid solutions (albumin).[29–31] Mounting evidence from these and other investigators demonstrated the benefit of plasma-based resuscitation (and the harm of albumin and crystalloid solutions) on coagulation, renal function, and cardiovascular (CV) response to hemorrhage. In this randomized trial, we found in the intent-to-treat analysis that mWB did not reduce transfusion volumes in severely injured patients requiring emergent transfusions compared with COMP therapy.

In their retrospective study of casualties treated in Afghanistan and Iraq, military investigators noted that implementation of a fresh WB program was associated with a reduction in blood component use.[26] Israeli researchers demonstrated in postoperative cardiac surgery patients that fresh WB was superior to COMP therapy with respect to estimated blood loss, platelet transfusions, and platelet aggregation.[32] Ho and Leonard[33] recently evaluated their experience in Australia in a mixed population of patients (trauma, cardiac, obstetrics) receiving WB and COMP therapy. They noted that despite improved coagulation profiles, WB was not associated with decreased blood utilization. In this study, the primary outcome of interest (and the one on which the study was powered) was 24-hour blood product utilization. We found that in both the intent-to-treat and per-protocol analyses, WB was not superior to COMP therapy in blood product utilization. There was, however, a trend toward less plasma and platelet transfusions in the first 3 hours among WB subjects. The lack of statistical significance may represent a type II error.

A critical difference, however, exists between the products used in these studies and in the current pilot study.[25,32,34] Although the military experience was with warm, fresh WB, we used modified WB that was not fresh and did not retain native platelet function for reasons stated in the "Materials and Methods" section.[34] This major difference could account for the discrepancy in these studies. However, our product is similar to that used in studies from Harborview in the 1980s.[13,14] In those studies, the investigators used modified WB that was prepared by actively removing platelets and cryoprecipitate from the product. During preparation of the modified WB units in this study, platelets were removed from our WB units by a leukoreduction filter system, which was required by the sponsoring agency (DoD). In addition, cryoprecipitate was not removed from our individual WB units. In their mixed population study (patients with trauma, gastrointestinal hemorrhage, and aortic aneurysm), the Harborview investigators randomized 41 patients who had been transfused at least 12 units of modified WB to receive either supplemental plasma or platelets.[14] Among this critically ill group of patients (mortality rate, 60%), the investigators noted that patients receiving supplemental platelets transfusions had a trend toward shorter duration of shock/hypotension and received less resuscitation volumes (both $P < 0.10$). There was no difference in survival.

As noted in the "Materials and Methods" section, soon after beginning the trial, we noted that a considerable number of patients with severe TBI had been enrolled. In addition, despite randomization and blinded group assignment, a disparate number of patients with TBI were enrolled in the WB arm. Not surprisingly, univariate analysis demonstrated that WB subjects had lower Glasgow Coma Scale scores, higher head AIS scores, and higher incidence of nonsurvivable TBI. To address this, a sensitivity analysis was performed to assess the primary and secondary outcomes of patients without severe TBI (AIS score <3). We found that in patients without severe TBI, WB significantly reduced transfusion volumes of RBC and plasma and other blood products. In addition, there was a strong trend toward reduction in 24-hour platelet transfusions ($P = 0.09$). These findings are not surprising given that resuscitation endpoints (not incorporating permissive hypotension) and approaches to coagulopathy (use of platelets and plasma for more subtle abnormalities on coagulation testing) in these patients differ quite significantly from that of traditional damage control resuscitation strategies.

Despite being a randomized controlled trial, this study has several limitations. First, although this was a single-center, pilot study intended to assess the impact of WB on transfusion volumes, it was also designed and intended to examine the feasibility of conducting a WB trial of bleeding patients, using Exception From Informed Consent. Moreover, it was an examination of the ability to randomize and use WB in a civilian setting. Second, as noted previously, we failed to specifically exclude patients with severe TBI from our initial protocol. Not surprisingly, several patients with severe and even nonsurvivable TBI were randomized early on in the study. Next, we did not use an objective scoring system in this study to randomize patients and, therefore, did not always include patients who would have received an MT. Learning from this, we incorporated a validated screening tool (ABC score) to identify patients for randomization in our current transfusion study, Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR)—a multicenter, randomized trial of blood

product ratios.[35,36] Finally, from this study's initial design to its first randomized patient, almost 4 years elapsed. During this time frame, our center's standard of care and faculty experience and expectations for patients in hemorrhagic shock changed dramatically. Our MT protocol underwent significant alterations, initial MT protocol cooler delivery was reduced to less than 10 minutes, and blood and plasma were immediately available to us in the ED. Therefore, when faced with an additional delay for WB randomization (an additional 5–10 minutes for blood typing), trauma faculty often excluded the sickest patients from the study, opting for delivery of the first MT cooler in a more timely fashion (within 10 minutes vs 15–20 minutes).

CONCLUSIONS

Compared with COMP therapy, WB did not reduce transfusion volumes in severely injured patients predicted to receive MT. As well, both 24-hour and 30-day mortality were similar between groups. However, in patients without severe brain injuries, WB significantly reduced RBC, plasma, and overall transfusion volumes.

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DISCUSSANTS

Donald D. Trunkey (Portland, OR):

This is a good but not a perfect study. I think you would acknowledge that.

Reading your methods is very painful, because you went from 1695 patients down to 55 who received the modified whole blood, including the components. There was a troubling trend, with a lower Glasgow Coma Scale score and a higher brain AIS score, and thus a higher international normalized ratio, in the whole blood studies. Brain tissue has the highest level in the tissue of thromboplastin. Did you measure the circulating thromboplastin?

You also compared your study with the military experience. You wrote, "While the military experience was with warm, fresh whole blood, the current trial used modified blood that was not fresh and did not retain the native platelet function." I think this is a major difference that could account for the discrepancy in these studies.

In August 1966, I was discharged from the Army. I went to San Francisco to start my surgical residency. Bill Blaisdell had been appointed the chief of San Francisco General that July 1. He had already changed the way we would transfuse patients with trauma.

The blood bank was in the San Francisco Medical Society building. There was a wonderful hematologist by the name of Herb Perkins. They saved one-third of every day's supply of whole blood. They put it in the refrigerator at 4 PM, and if we did not use it that

night, it was turned into components the following day. So we had whole blood 365 days a year.

In addition, there were 800 policemen who were on duty at any given time in San Francisco. If we wanted fresh, whole warm blood, we could bring in whatever we needed by radioing these cars, and they would come and respond. Similarly, we bled residents, we bled medical students, we bled firemen, and we bled faculty surgeons.

So, we could get whole blood. I think that in future studies, it would be nice to have real whole blood that was warm, because I think the military has shown that this is the ideal for reducing mortality and morbidity.

Response From Bryan A. Cotton:

We couldn't agree more about the fresh, warm whole blood and the differences with our modified component. Considering the time when we implemented this study, I think we were very spoiled that we even had a blood center that was open to conducting a blood trial such as this and allowing us to have whole blood.

Fractionation or component therapy is a much more economic and business–friendly model. Fractionation of whole blood into its components is often equated to stealing a car and chopping it up into parts; you can not only make more money selling the parts than selling the whole car but also serve more people. To disrupt the process of using blood components by asking them to do this whole blood was a big undertaking. I think doing it in a fresh, warm whole blood in the future would be beneficial and I advocate it. It also brings back the platelets and their activity in contribution.

As far as the circulating levels and factors and cytokines, that analysis was captured. We had a very robust laboratory core that was developed for this at the ISR in San Antonio, with Par Johansson in Copenhagen, Denmark, and in San Francisco with Mitch Cohen. And that work and data are ongoing, and we look forward to actually having that data soon.

DISCUSSANTS

M.A. Schreiber (Portland, OR):

One of the big problems with fresh whole blood is storing it. Each of the components of the fresh whole blood has different storage requirements. So, my first question for you is how long can you store this modified whole blood?

Response From B.A. Cotton:

The modified whole blood can be stored up to 5 days.

DISCUSSANTS

Charles E. Lucas (Detroit, MI):

This is another wonderful study on coagulation from the University of Texas at Houston. Dr Cotton, last month we reported data that suggest that the process of freezing plasma causes alterations in proteins and procoagulants so that when these procoagulants are thawed and administered to severely injured patients, they cause alterations in the interstitial fluid space dynamics, resulting in an increase in the sequestering of fluid in the interstitial space. We're looking at data now that further support that effect, which is not seen in canine studies.

So my question is, did you look at the amount of crystalloid solution that you gave to your patients in the first 24 hours after operation to see whether the patients who received the thawed plasma required increased crystalloids?

Response From B.A. Cotton:

To respond to Dr Lucas, regarding the effects of the freeze/thaw process, our centers and several other centers have shown that, by doing that, you do impact the plasma efficacy and hemostatic potential and endothelial leak or glycocalyx disruption.

To answer Dr Lucas' question, we did not have a difference in our resuscitation volumes of crystalloid in the first 24 hours, which was minimal, in the $3\frac{1}{2}$ to 4-L range.

DISCUSSANTS

M.A. Schreiber:

A 5-day storage time raises a huge issue for logistics and blood banking. Red cells can be stored for 42 days and plasma can be stored for a year. If we were to use this product, we would not have adequate blood products to treat our patients with trauma. In the absence of a clinical benefit, I would argue that this is not a beneficial way to go.

Response From B.A. Cotton:

To answer Dr Schreiber's question, I agree that this is a tremendous task to place on blood banks and blood centers. That said, utilizing modified whole blood in select patients in massive transfusion settings may very well be viable. The 5-day window does bring a lot more to the table. And that 5-day window, in a busy enough center, whether it's from trauma or obstetrics or CV, could utilize this in a wise fashion, using that 5-day window, not starting with that blood product, obviously, but utilizing it with second and third cooler disbursements.

DISCUSSANTS

Christopher C. Baker (Roanoke, VA):

I echo Dr Trunkey's comments. When I was a resident in San Francisco in the 1970s, we had the products he described, and when I moved to Yale, all of a sudden, coagulopathy came to be a much bigger problem. So, I think that it is a good goal.

Can you give us the range of transfusions? Because, based on the numbers in your abstract, it doesn't look what I would call massive transfusion.

Response From Bryan A. Cotton:

The range of transfusions for median units transfused was in the massive range. It was 11 to 16, 11 in the whole blood arm and 16 in the component blood arm. Once you broke it up into those who were actually resuscitated, not just in the intent-to-treat or per protocol groups, the volume goes up. And if you actually break it up into our sensitivity analysis, excluding those with severe head injuries, the transfusion volumes go up dramatically again to the median of about 11 units in whole blood and 16 in the component arm.